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Cognitive problems related to epilepsy syndromes, especially malignant epilepsies

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Summary Neurocognitive impairment is frequent in epilepsy patients. Causes are multiple, and may be influenced by several factors including the epilepsy syndrome.

Most cognitive complaints in adult patients are mental slowness, memory difficulties and attention deficits. In children, cognitive problems are more diffuse, responsible for language troubles, learning difficulties, poor academic outcome, behavior problems and finally unfortunate socio-professional prognosis.

The most devastating epilepsy syndromes such as epileptic encephalopathies are nearly exclusively described in infancy and childhood.

This paper will review the major cognitive complaints in relation to the epilepsy syndrome, with a more detailed interest for the malignant epilepsies in infancy and childhood such as Ohtahara and West syndrome, Lennox-Gastaut syndrome and epileptic encephalopathis with continuous spike-and-wase during slow wave sleep.

The impact of surgery on cognition will be briefly discussed in adults and youger patients.

Introduction

Epilepsy is a symptom rather than the cause of brain dysfunction. The most prominent feature of epilepsy are the seizures, but mental health may be also involved, including memory deficits, learning disabilities, behavioral problems, and poor social outcome.

Epileptic seizures can cause both morphological and functional changes within the brain as well as cognitive and neuropsychological alterations. The short- and long-term consequences can be influenced by several factors, especially the epilepsy syndrome.

Abbreviations: BECTS, benign childhood epilepsy with centrotemporal spikes; CSWS, continuous spike-and-wave during slow sleep; EEG, electro-encephalogram; ESES, electrical status epilepticus during slow sleep; LGS, Lennox-Gastaut syndrome; LKS, Landau–Kleffner syndrome; MRE, malignant rolandic epilepsy; (f)MRI, (functional) magnetic resonance imagery; MTL, mesio-temporal lobe; SW, spike-and-wave

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If most of the changes are transient and seizure-related, mental health problems may persist even if the patient achieved seizure freedom or may be present with a history of a few seizures. Major cognitive complaints will be reviewed in regard to the epilepsy syndrome, with a particular attention to the malignant epilepsies in infancy and childhood.

The impact of medical treatment and psychiatric-related cognitive problems will not be discussed in this paper.

Definitions

Cognition can be defined as the capacity of the brain to process information accurately and to program adaptive behaviour.

Cognition involves the ability to solve problems, to memorize information, or to focus attention. On a higher level, it involves dealing with complex situations creatively by transcending from the immediate circumstances to anticipate future acting.

An *epileptic* or *epilepsy syndrome* is a cluster of seizures, other symptoms, physical signs and laboratory findings, which are associated in a non-fortuitous manner.

Identification of an epileptic syndrome requires clinical findings (type of seizure, age at onset, precipitating factors, severity and chronicity, circadian distribution, aetiology, anatomical location and prognosis) and data from ancillary studies (electro-encephalogram (EEG), brain anatomical and metabolic imaging, haematology and biochemistry).

Epileptic encephalopathies or malignant epilepsies are clinical situations where the (sub)continuous epileptiform discharges induce absence of cognitive development or mental stagnation followed by regression as long as they persist. Several syndromes have been recognised by the international classification (Table 1) according to the underlying pathology, age of onset, seizure type and EEG pattern.

Malignant rolandic epilepsy (MRE) is not yet recognised as a specific syndrome. Nevertheless, some idiopathic ''benign'' idiopathic partial epilepsies have been recognised to be able to develop a malignant course. This specific evolution should be classified as an epileptic encephalopathy.

In the literature, there is confusion about the definition and occasionally contradictions exist between reports. This is because the same wording is used sometimes only for the EEG pattern and sometimes for the clinical syndrome.[1]

Cognitive problems in epilepsy

The most reported cognitive complaints in adults are mental slowness, memory impairment and attention deficits.

However, because early seizures can induce permanent deficits and increase seizure susceptibility and that prolonged exposure to abnormal neural activity during a critical period of cerebral maturation may disrupt the structural and functional changes in the brain, diffuse impairments[2] are more often documented in children with additional troubles (compared to adults) such as learning disabilities, poor academic outcome, behaviour problems, and language stagnation or deterioration.

Some brain ''structures'' develop into late adolescence (such as the prefrontal cortex) and therefore, time is needed to observe a number of deficits in childhood epilepsy. Therefore, the long-term follow-up becomes a complex situation, difficult

Table 1 Electro-clinical characteristics of major epileptic encephalopathies

	Ohtahara/West	Lennox-Gastaut	CSWS	Malignant rolandic	Landau—Kleffner
Age of onset	First months of life	2—4 years	4—5 years	Before 6 years	3—8 years
Main seizure type	Epileptic spasms	Atypical absences, myoclonic, tonic	Often nocturnal at the beginning; both partial and generalized	Sensorimotor focal, often nocturnal	Rare and occasional, often nocturnal
EEG pattern	Burst-suppression/ hypsarhythmia	Slow SW, fast activities	ESES	ESES	ESES
Usual abnormal area	Posterior	Anterior	(Pre)frontal	Central	Parieto-temporal
Aetiology	Symptomatic in most cases	Symptomatic, about 30% cryptogenic	Cryptogenic, sometimes symptomatic	Cryptogenic	Cryptogenic in most of cases

CSWS, continuous spike-and-waves during sleep; ESES, electrical status epilepticus during sleep; SW, spike-and-wave.

to analyse. Indeed, not only epilepsy and seizures have negative impact, but the evolution is complicated by adverse events related to the therapy; by negative academic, social and professional impact of seizures and by psychiatric or organic comorbidities.

Seizure types, EEG findings, age at onset, severity and chronicity of the syndrome, anatomical location and aetiology are the principal aspects of the definition of an epileptic syndrome. Each of these parameters may have a specific influence on cogntition.

Age at onset "per se" is not a pejorative factor, benign myoclonic epilepsy of infancy being a good example. However, in a specific situation as temporal lobe epilepsy, an earlier onset is associated with a worse prognosis.[3,4]

One could consider that "major" seizures are more deleterious than "minor" seizures for brain development. Tonic or tonic–clonic seizures may have a negative impact if prolonged or because the risk of repetitive head trauma. On one hand, epileptic spasms and tonic seizures are always observed in severe and refractory epilepsies, but the negative impact of these seizures is not specifically related to the seizure type. On the other hand, some "minor" seizures as atypical absence or repetitive non-convulsive status may have a negative effect on cognitive development.

The aetiology is a very important factor. Idiopathic (genetic) epilepsy patients develop better than cryptogenic/symptomatic cases. However, this general assertion suffers from some exceptions, for example Dravet syndrome is a genetic epilepsy syndrome with a severe prognosis, while some cryptogenic focal epilepsies may have a favourable evolution with a fast and complete seizure control and no cognitive deficits.

Finally, among these factors, severity and chronicity are the major sources for cognitive problems,[3] while anatomical location explains the specificity of these symptoms.

The pre-seizure condition or (co)existing behavioural problems should not be underestimated. Indeed, some studies showed that in newly diagnosed and untreated epileptic patients, cognitive problems are already present[5–7] in more than 50% of patients. Lastly, the final outcome is also related to the parents' ability to continue habitual parenting.[8]

Finally, greater neural plasticity does not necessarily imply adaptive plasticity. During early childhood and infancy, localisation of competences might be more diffuse than they are later, but also competences might be less differentiate one from other.

Higher cognitive functions, undergoing development and maturation, are most vulnerable to the effects of seizures and (inter)ictal epileptiform discharges, most likely due to their greater neurodevelopmental plasticity.

Memory impairment

Memory problems are more marked in focal compared to generalized epilepsies, particularly short-term memory. The impairment is related to the laterality with a verbal learning deficit in the dominant lobe and a figural learning deficit in the non-dominant lobe.

Impairment is more pronouced in dominant mesio-temporal lobe (MTL) epilepsy, with the severity of the deficit negatively correlated with the length of active epilepsy.

However, memory deficits are also described in extra-temporal epilepsy, such as frontal lobe epilepsy.[9] Attention and language problems may be, at least in part, responsible for the memory deficits.

Memory deficits in children belong to a more diffuse impairment and are rarely described as such.

Attention and executive function deficits

Attention is a neuropsychological construct that defines the processes involved in perception, selection, and maintaining or detaching from stimuli. Impairment of sustained attention is most consistently described in epilepsy[10] and is more significant in predicting academic failure than memory or socioeconomic factors.[11]

(Pre)frontal lobe dysfunction is responsible for disturbances in executive functions by direct dysfunction (epilepsy focus) or indirect due to the seizure spread and secondary abnormal circuitry.[12] Frontal lobes seem to be the preferred target of ictal and interictal spreading of focal epilepsy[13] as well as idiopathic generalized epilepsies.[14]

Frontal lobe functions, or more precisely executive functions, develop through adolescence.

These facts together could explain that attention and executive function deficits are impaired whatever the syndrome, especially in younger patients.

Language dysfunction

Children tend to be more impaired than adults. More common language problems are poor lexical knowledge, word-finding difficulties and anomia.[15] However, there is evidence that reading and spelling are also affected. This may be attributable to atypical language distribution with increased right activation. Using functional magnetic resonance imagery (fMRI) in epilepsy patients, several language patterns differ from normal control with atypical language activation in about one-third of patients or

atypical language dominance in one-fifth of patients.[16] This reorganization is more likely to occur with epilepsy onset before 6 years of age; however, late reorganization has been described in specific cases as in late-onset left Rasmussen syndrome.[17]

Some Wada-test and fMRI studies[18] showed that higher interictal spike frequency (>20 interictal discharges/h) as well as temporo-posterior seizure involvement is associated with atypical speech location.

Patients with atypical language location had better cognitive measures, suggesting a deleterious cognitive effect on those unable to transfer and compensatory mechanisms on those able to delocate.[19,20]

Epileptic encephalopathies

These encephalopathies (Table 1) have common features of cognitive function: arrest of development and then regression. The effect of a damaging neural process will depend on the state of maturation of the brain in which it occurs. Maturation might proceed simultaneously in several connected and active cortical regions, involving a functional maturation of networks rather than area by area. Several studies have shown that after a unilateral perinatal brain lesion, whatever the side, speech development is delayed.[21] fMRI studies showed that language develops sometimes in the controlateral hemisphere or sometimes in regions next to the lesion[22] without satisfactory explanation for these differences. These epileptic encephalopathies may also have major impact on language and social performances and may be responsible of the so-called "autistic regression".

Cognitive impairment caused by interictal epileptiform discharges is specific and reflects the functional disturbance of the area where the spikes originate or spread.

All epileptic encephalopathies will not be discussed, as epilepsy related to hypothalamic hamartoma, or ring 20 chromosome epilepsy, for example.

Ohtahara and West syndromes

These epileptic syndromes are classified as cryptogenic/symptomatic generalized epilepsy, but in fact some of them may have a focal or regional lesion. They are characterised by an early onset (first few weeks or months of life), epileptic spasms and neurodevelopmental delay or regression. EEGs are diffusely and highly abnormal.

During the first months of life, infants develop especially visual attention and visuo-auditory-social competences[23–25] and therefore, it is not surprising to observe that one of the major interictal signs is loss of visual contact and smile. In early infantile epileptic encephalopathies, specific questions can reveal that these infants never had visual contact, while in West syndrome some infants may have an apparent normal development during the first few months or weeks of life.

If the seizures are not stopped rapidly with a normalized EEG, the infants will develop a further autisitc behavior, which will persist for life even if their epilepsy is finally stabilized.

Lennox-Gastaut syndrome (LGS)

"Lennox syndrome" or "childhood epileptic encephalopathy with diffuse slow spike-and-waves" is defined as a cryptogenic or symptomatic generalized epilepsy, even if in some cases there is a focal driver. LGS is a devastating epilepsy syndrome constituting 1—4% of childhood epilepsies and is characterized by multiple seizure type, mental retardation or regression, and generalized slow SW discharges (1.5—2 Hz). Seizures often are resistant to therapy and severe mental handicap with behavioural problems is not an exceptional outcome.

In this particular syndrome, causes of cognitive regression are multifactorial: high seizure rate, numerous head trauma related to epileptic drop attacks, continuous SW discharges during all sleep stages, polytherapy, etc. However, global prognosis is better if seizures can be controlled and EEG improved early by the treatment.

Malignant epilepsies with ESES

Two recognised syndromes (CSWS and Landau—Kleffner syndrome (LKS)) and another syndrome (MRE) have a common EEG feature (ESES), a poor cognitive outcome with permanent deficit, and only few, especially nocturnal, focal seizures in most cases, but no seizures in about 25—30% of patients. These three clinical syndromes (Table 2) start during childhood, around 6 years of age and they all are refractory to usual medical treatment.

The prominent focus is more anterior in CSWS, posterior in LKS, and central in MRE. More recently, a fourth more posterior type is emerging with atypical evolution in a few patients with initially typical early-onset benign childhood occipital epilepsy (Panayiotopoulos type) syndrome. Language impairment appears, secondary to ESES registered in these

Table 2 Clinical symptoms and syndromes related to ESES

	CSWS	Malignant rolandic epilepsy	Landau—Kleffner syndrome
Aetiology	Cryptogenic (normal development before) or symptomatic (pre-existing encephalopathy)	Cryptogenic (gliosis or dysplasia if cortical excision performed)	Rarely symptomatic
Motricity	Dyspraxia, dystonia, ataxia, or unilateral deficit		Bizarre automatisms
Attention	Reduced attention span	Difficulties to maintain	Deficits
Memory	Poor performance	Difficulties in verbal learning and working memory	Residual impairment in verbal short-term memory
Executive functions	Impaired temporospatial orientation		Preserved at the beginning
Behaviour	Aggresiveness, hyperkinesia	Hyperactivity	Excitability, hyperactivity
Language	Expressive aphasia	Dysarthria or dysphasia	Auditory agnosia, acquired aphasia
Seizures	Often nocturnal seizures at the beginning; both partial and generalized: unilateral or bilateral clonic, generalized tonic—clonic, absences, focal motor, focal with impaired consciousness or epileptic falls; never tonic	Somatomotor often nocturnal at the beginning; then negative myoclonus during wakefulness, atypical absences, epileptic falls, occasional secondary generalization	Eyelid myoclonia, eye blinking, atypical absences, head drops and atonic fits in upper limbs, automatisms, and occasionally, partial motor seizures with secondary generalization

CSWS, continuous spike-and-wave during slow sleep.

children.[26,27] However, this last syndrome will not be further discussed because of paucity of the data.

These all may be considered as a continuum (Fig. 1), with a strict association between the pattern of neuropsychological defect and the location of the epileptiform focus.[28] In these epilepsies, the term "focus" should be considered more as a regional epileptogenic zone than as a strictly local focus as defined in MTL epilepsy for example.

However, in these three conditions, all children develop impulsivity, inattention, learning or behavioral disorders independently of the driver focus. Attention is subserved by complex networks distributed in the frontal lobes and by a functional balance between the two hemispheres. These anatomico-functional circuits mature between early childhood and adolescence. These epilepsy syndromes develop in the same period of brain maturation and appear

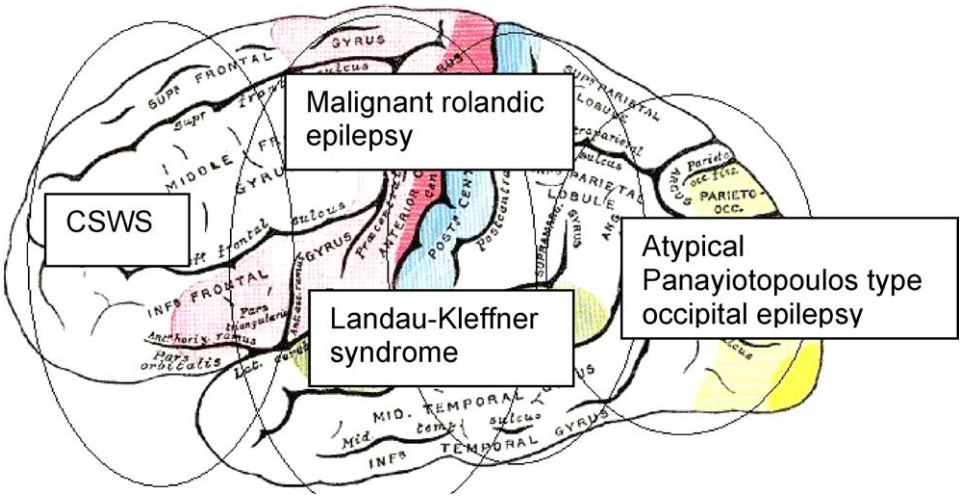

Figure 1 Epileptic encephalopathies or malignant epilepsies with electrical status epilepticus during sleep. Pathophysiology is quite the same, but symptoms are defined by the driver focus: prefrontal and frontal area in continuous spike-waves syndrome (CSWS), central region in malignant rolandic epilepsy, temporo-parietal location in Landau—Kleffner syndrome or more posterior in atypical Panayiotopoulos type occipital epilepsy.

to interfere with the setting up of attention abilities, whatever the location of the focus.

On the other hand, disturbances of higher cortical functions were strongly correlated with morphology, organization, and location of epileptiform abnormalities.

Finally, some patients suffer from different symptoms overlapping this classic syndromic classification and therefore, remain unclassified.

Continuous spike-waves during sleep syndrome (CSWS)

The clinical manifestations of this syndrome include several seizure types, a constant and severe deterioration of neuropsychological functions associated with a decline of motor abilities with appearance of dystonia, ataxia, or unilateral deficit. The typical EEG pattern of ESES, occupying often 85—100% of slow sleep, is also an essential and absolute feature for the recognition of the syndrome.

Children may have either a normal psychomotor development or abnormal signs indicating pre-existing encephalopathy. The good final seizure outcome is independent of the aetiology. Language capacity can be particularly affected in cases showing the predominance of paroxysmal abnormalities over temporal regions, while behavioural problems, hyperkinesis and even psychosis are found in children exhibiting interictal frontal foci or clear-cut anterior predominance of the discharges.

Malignant rolandic epilepsy (MRE)

This epilepsy syndrome is sometimes described as a subgroup (atypical) of benign epilepsy with rolandic or centrotemporal spikes (BECTS) showing a malignant course,[29] sometimes as a specific syndrome.[30] However, they are also classified as CWSW or LKS by some authors because the patients present bilateral ESES with cognitive and behavioral impairments.

However, these patients have complementary symptoms to classical BECTS as brief myoclonic or atonic seizures, long-lasting cognitive deficits and bilateral ESES. Therefore, they no longer meet the definition of benign epilepsy characterized by onset in childhood, absence of demonstrable brain lesion, infrequent and brief partial seizures, paradoxically abundant interictal EEG abnormalities, and spontaneous remission before the end of adolescence.

In the operated cases, anatomopathological studies show micro-dysplasia[30] and therefore, these cases do not meet the definition of "idiopathic" and should be considered as cryptogenic. It is therefore also useful to distinguish this syndrome from BECTS for the aetiologic point of view.

Landau—Kleffner syndrome (LKS)

In 1957, Landau and Kleffner described six children with a "syndrome of acquired aphasia with convulsive disorder".[31] The 1989 International League Against Epilepsy placed this syndrome under the classification of epilepsies and syndromes undetermined as to whether they are focal or generalized. Finally, this syndrome is considered to belong to the epileptic encephalopathies as proposed by ILAE's Task Force on Classification.[32]

The classic features of LKS include a previously healthy child with normal language acquisition, followed by a verbal auditory agnosia (i.e., word deafness), language regression, seizures, and an epileptiform EEG with ESES during night.

Pathologic specimens obtained after surgical procedure have demonstrated subcortical astrocytosis, perivascular lymphocytosis, and microglial nodule formation or excessive ectopic neurons. These findings demonstrate a pathologic process in these anatomic regions even if MRI is normal.

Impact of surgical treatment

In focal epilepsies

It appears that lateralized memory problems are more readily demonstrable in post-temporal lobectomy than in nonsurgical patients,[33] especially in adults.

Cognitive improvement in seizure-free patients after surgery indicates that an epileptic process was active before surgery and caused a persistent functional change in cognition on local and distant functions.[34] These functional changes can have irreversible consequences in children if they fall into particular sensitive periods of development.

Little discernible change in cognitive function can be attributed specifically to surgery in the short term,[35,36] but successful surgery may stabilize cognitive decline over longer follow-up periods.[37] On the other hand, significant memory recovery have been described at 12 months after surgery in some patients, suggesting that recovery is driven by functional reorganization. Results on cognitive functions are, however, inversely correlated to the length of epilepsy before surgery. Otsubo et al.[30] do not note significant cognitive improvement in his series, even for patients achieving seizure freedom. But they waited for at least 5 years of refractoriness because of presurgical evaluation. Their poor results could be explained by the long delay in a critical period of vulnerability.

It is always surprising to observe that surgical treatment of focal epilepsies in children usually

improves very fast alertness, mood, and attention while in adults the improvement is delayed if it happens at all. The disappearance of an (abundant) interictal epileptiform activity secondary to surgery may allow the recovery of functional disorders of the complex network of neurocognition in children while, in adults, because of longer duration of the epilepsy and the end of active neuroplasticity, cognitive impairments became secondary to structural damage and therefore less reversible.

In epileptic encephalopathies

In 1995, Morrell et al.[1] showed that the technique of multiple subpial transections of the cortex is able to abolish epileptic discharges in a series of 14 children with acquired epileptic aphasia who had been unable to use language to communicate for at least 2 years. Sustained improvement was obtained in 11 of them. According to the authors, success depends on selection of cases having severe EEG abnormality that can be demonstrated to be unilateral in origin. In a more recent small series,[38] five children with LKS aged 5.5—10 years underwent multiple subpial transections, and behavior and seizure frequency improved dramatically. Improvement in language also occurred in all children, although none of them reached an age-appropriate level of language even when their electrical status epilepticus during sleep was eliminated by the procedure.

In our series of six surgical cases of epileptic encephalopathies (two LGS, one LKS, one CSWS, two MRE) treated with multiple subpial transections and sometimes additional cortectomy, none have been worsened by the surgical procedure. Three (one LGS, one CSWS, one LKS) were notably improved for the ictal and interictal status, while the three others had an important seizure decrease, but no significant improvement for cognitive functions. However, all these cases arrived lately to surgery after numerous years of intractability and severe cognitive deterioration.

Conclusions

Epilepsy is more than seizures. An ongoing epileptogenic process can irreversibly damage the brain, especially maturing brain, even if seizures are controlled or missing, and causes persistent cognitive changes and finally global intellectual deficits.

Early and complete seizure control and EEG normalisation is mandatory for the prevention of developmental disablement in younger patients or of accelarated cognitive decline in adults and older patients.

The adequate treatment should not be limited to antiepileptic drugs. Surgical treatment may be an option in selected refractory cases, but the success will be higher if surgery is performed earlier.

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